

## **Remarks**

### **I. Addressing the Examiner's Objections And Rejections.**

#### **1. Objection to the Priority Claim.**

Applicants thank the Examiner for the Examiner's careful attention to the contents of the specification. Applicants have amended the priority claim to provide proper phrasing.

#### **2. Consideration of the Reference of Davies, et al.**

In the Office action, the Examiner stated the following:

Reference AC-4 by DAVIES et al. was not received with the IDS and has not been considered. (Office action, dated 22 September 2003, page 2, second full paragraph.)

It is unclear to applicants why the Davies, et al., reference was not with the file when the Examiner reviewed the file. Applicants' records indicate that all six references were submitted with the Supplemental IDS, mailed 12 June 2003 and received by the USPTO on 16 June 2003 (e.g., see Appendix A, copy of "Information Disclosure Statement under 37 C.F.R. §1.97," which was mailed with the 1449 reciting Davies, et al., stating: "Copies of the information and a completed Form PTO-1449 listing the references accompany this paper."). Accordingly, applicants believe no further IDS-associated fee is due. Accompanying this paper is an additional form 1449 and a copy of the Davies, et al., reference (Appendix B). Applicants request that the Examiner make Davies, et al., of record in the present application.

Although applicants believe no further fee should be due, the Commissioner is hereby authorized to charge to Deposit Account No. 03-4058 any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, with the exception of the payment of the issue fee.

#### **3. Objection to the Priority Claim.**

The Examiner objected to claim 10 because of the following informalities:

the term "reservoir" in line 2 should be --reservoirs-- (Office action, dated 22 September 2003, page 3, second full paragraph).

Applicants thank the Examiner for the Examiner's careful attention to the language of the claims. Claim 10 is amended herein pursuant to the Examiner's request.

**4. Rejection of Claims 8 and 9 under 35 U.S.C. §112, Second Paragraph.**

The Examiner has rejected claims 8 and 9 under 35 U.S.C. §112, second paragraph, asserting that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner asserted that there is insufficient antecedent basis for the limitation "the sampling system."

Once again, applicants thank the Examiner for the Examiner's careful attention to the language of the claims. Claims 8 and 9 are canceled by this amendment; thus obviating the basis for this rejection.

In view of applicants' cancellation of claims 8 and 9, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

**5. Rejection of the Claims Under 35 U.S.C. §103(a).**

The Examiner has rejected claims 1-34 under 35 U.S.C. §103(a) asserting that the claims are unpatentable over Kurnik (WO 99/58973) in view of Tamada, et al. (JAMA 282(19):1839-1844, 17 November 1999).

The PTO has the burden of establishing a case of *prima facie* obviousness and can meet this burden "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fine*, 837 F.2d 1071, 5 USPQd2 1596 (Fed. Cir. 1988).

Applicants respectfully traverse the Examiner's rejection of the claims for the following reasons. The present invention relates to a multiple step approach to predicting a hypoglycemic event in a subject when **both** (i) comparing a predicted measurement value to a threshold glucose value indicates a hypoglycemic event at a further time interval, **and** (ii) comparing a parameter value or trend of parameter values with a threshold parameter value indicates a hypoglycemic event, wherein at least one of the parameters is skin conductance or temperature of the subject.

Kurnik teaches a method and device for predicting a future or past concentration of an

analyte using a series of measurements obtained from a monitoring system. One application of the teachings of the Kurnik reference involves predicting future or past blood glucose concentrations. (See, for example, Kurnik, page 1, lines 6-12.) In one particular aspect of the Kurnik reference, a raw signal is obtained using a transdermal sampling system that is placed in operative contact with a skin or mucosal surface of a biological system (e.g., Kurnik, page 3, lines 22-25). It is only in the context of a monitoring system comprising an exemplary transdermal sampling device (i.e., an iontophoretic glucose sampling device) that skin conductance and temperature are discussed in the Kurnik reference. In the Office action, the Examiner stated the following:

KURNIK further teaches that both perspiration (sweat) and skin temperature may be monitored before, during, and after glucose measurement, and teaches that perspiration may contain glucose (p. 43, lines 7-22). (Office action, dated 22 September 2003, page 6, first full paragraph.)

The teachings concerning both perspiration and temperature, referred to by the Examiner, are “(i)n the context of the iontophoretic glucose sampling device described hereinabove” (Kurnik, page 42, lines 30-31). These teachings relate only to variables, including sweat and temperature, that may affect the functioning and accuracy of the iontophoretic glucose sampling device. Kurnik in no way relates these variables to prediction of a hypoglycemic event at a future time. For example, noting that perspiration contains glucose (Kurnik, page 43, line 7), the Kurnik reference stated the following in context:

For example, perspiration contains glucose, and perspiration occurring rapidly and in sufficient quantities **may affect the detected signal either before or during biosensor measurement** (emphasis added; Kurnik, page 43, lines 7-10).

This interpretation of the reference is confirmed by the following teaching in the Kurnik reference:

The housing 32 can further include an optional temperature sensing element (e.g., a thermistor, thermometer, or thermocouple device) which monitors the temperature at the collection reservoirs **to enable temperature**

**correction of sensor signals.** The housing can also include an optional conductance sensing element (e.g., an integrated pair of electrodes) which monitors the conductance at the skin or mucosal surface **to enable data screening correction or invalidation of sensor signals** (emphasis added; Kurnik, page 32, line 28, to page 33, line 5).

The Kurnik reference neither teaches nor suggests a multiple step approach to predicting a hypoglycemic event in a subject when **both** (i) comparing a predicted measurement value to a threshold glucose value indicates a hypoglycemic event at a further time interval, **and** (ii) comparing a parameter value or trend of parameter values with a threshold parameter value indicates a hypoglycemic event, wherein at least one of the parameters is skin conductance or temperature of the subject.

In *Bausch & Lomb v. Barnes-Hind/Hydrocurve* (796 F.2d 443, 230 USPQ 416 (Fed. Cir. 1986)), the U.S. Court of Appeals for the Federal Circuit emphasized the following:

It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art.

The reference of Tamada, et al., does not make up for any of the shortcomings of the Kurnik reference relative to the presently claimed invention. Regarding the Tamada, et al., reference, the Examiner asserted the following:

TAMADA teaches a system and method for monitoring glucose levels in a subject wherein an alarm is sounded if glucose levels fall below a user-selected threshold (alert level, p. 1839) and/or if skin conductance and temperature values exceed set thresholds (p. 1841). TAMADA specifically teaches that both sweat and temperature fluctuations are associated with glucose measurements, and teaches that both skin conductance measurements and glucose measurements are compared to thresholds and used to predict/indicate hypoglycemia (p. 1841).

It would have been obvious to one of ordinary skill in the art to have compared both the glucose prediction and measured parameter values (sweat and skin temperature) of KURNIK to threshold values, as taught by TAMADA, where the motivation would have been to reduce the risk of hypoglycemia and make therapy for diabetes safer and more acceptable to patients, as taught by TAMADA (p. 1840). It would have been further obvious to have used both glucose concentration prediction and measurement

of sweat/temperature, as taught by TAMADA, to predict a hypoglycemic event in the method and products of KURNIK where the motivation would have been to include parameters known to be associated with hypoglycemia, as taught by both KURNIK and TAMADA. (Office action, dated 22 September 2003, page 7, second and third full paragraphs.)

First, the reference of Tamada, et al., does not contain any teaching or suggestion of using a predicted measurement value at a further time interval to reduce the risk of hypoglycemia. The teachings of Tamada, et al., relate only to glucose values obtained in real time monitoring, i.e., glucose measurement values provided by GlucoWatch® (Cygnus, Inc., Redwood City, CA) biographers. The GlucoWatch biographer did not provide predicted glucose values at future time points. The teachings of Tamada, et al., relate to alarms based on **measured**, not predicted, glucose values (see, for example, Tamada, et al., page 1839, col. 1, second full paragraph). At page 1839, Tamada, et al., teach the following (emphasis added):

Automatic readings also provide the opportunity for an alarm to be sounded in response to values below a user-selected alert level or as a result of rapid declines in the **measured** glucose values. These alarms could provide a method to reduce the risk of hypoglycemia and make intensive therapy for diabetes safer and acceptable to more patients.

Second, the reference of Tamada, et al., does not contain any teaching or suggestion of combining a predicted glucose value from a further time interval with skin conductance or temperature threshold parameter values associated with hypoglycemia. As described above for the Kurnik reference, the reference of Tamada, et al., discusses skin conductance and temperature values as they affect sensor function in the monitoring device (i.e., the GlucoWatch biographer). In this regard Tamada, et al., teach the following:

#### Calculation of Glucose Value

The biographer contains sensors to measure skin temperature and conductance. The latter is directly related to the amount of sweat on the skin's surface. **Since the glucose in sweat can confound the measurement, if the skin conductance exceeds a predetermined threshold, the measurement for that cycle is skipped.** An alarm is sounded for both sweating and for hypoglycemia because the former is often associated with the latter. Similarly, **since temperature directly affects the sensor**

**operation**, if the temperature or time rate of change of the temperature exceeds predetermined thresholds, the entire (measurement) cycle is skipped. (Tamada, et al., page 1841, col. 1, first full paragraph.)

Accordingly, the reference of Tamada, et al., teaches no more than the reference of Kurnik and therefore does not make up for any of the shortcomings of the Kurnik reference relative to the presently claimed invention. The reference of Tamada, et al., does not contain any teaching or suggestion of using a multiple step approach for the prediction of hypoglycemic events (e.g., predicting a hypoglycemic event in a subject when both (i) comparing a predicted measurement value to a threshold glucose value indicates a hypoglycemic event at a further time interval, and (ii) comparing a parameter value or trend of parameter values with a threshold parameter value indicates a hypoglycemic event, wherein at least one of the parameters is skin conductance or temperature of the subject), nor does the reference provide any reasonable expectation of success for such an approach. In fact, the reference of Tamada, et al., defaults to the use of a single alarm for both sweating and possible hypoglycemia based solely on the presence of unacceptable levels of sweat ("An alarm is sounded for both sweating and for hypoglycemia because the former is often associated with the latter"). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Finally, even if, *in arguendo*, the elements of the present invention were taught in the prior art, the U.S. Court of Appeals for the Federal Circuit in *Symbol Technologies, Inc. v. Opticon, Inc.*, 935 F.2d 1569, 19 USPQ2d 1241 (Fed. Cir. 1991) stated the following:

We do not pick and chose among the individual elements of assorted prior art references to recreate the claimed invention, but rather, we look for some teaching or suggestion in the references to support their use in the particular claimed combination.

Prior to the teachings of the present specification, there was no indication in the prior art that one of ordinary skill in the art would predict a hypoglycemic event in a subject when **both** (i) comparing a predicted measurement value to a threshold glucose value indicates a hypoglycemic event at a further time interval, **and** (ii) comparing a parameter value or trend of parameter values with a threshold parameter value indicates a hypoglycemic event,

wherein at least one of the parameters is skin conductance or temperature of the subject. Obviousness requires some logical reason for combining the references at hand; otherwise, the use of the references will entail prohibited hindsight. See, for example, *In re Fine*, 837 F.2d 1071, 5 USPQd2 1596 (Fed. Cir. 1988); *In re Sernaker*, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983). Applicants respectfully submit that no motivation to combine the references, other than hindsight reconstruction, has been supplied by the Examiner.

In view of the arguments presented above, applicants submit that the Examiner has failed to establish a case of *prima facie* obviousness. Accordingly, applicants respectfully request that the rejections under 35 U.S.C. §103 be withdrawn.

### Conclusion

Applicants submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further communications in this application to:

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If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned at (650) 599-3526.

Respectfully submitted,

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